REMARKS/ARGUMENTS

Claims 1 and 3 have been revised to include the feature of a variable region from the daclizumab antibody. The sequence of the variable region is recognized in the art and known to the skilled person as disclosed in U.S. Patent 5,530,101 and described on page 94, lines 4-6, of the instant application. The revisions are made to better tailor the claims to currently contemplated commercial embodiments of the invention and so are made for business reasons. The revisions are not in acquiescence to any rejection of record. Applicants reserve the right to pursue the subject matter no longer within the scope of the amended claims in a continuing application without prejudice.

Claims 2 and 4 have been revised to include the feature of a heavy chain constant region from daclizumab.

Support for the revisions to claims 1-4 is found in the instant application at least from page 23, line 16, to page 24, line 16, and in Figure 22.

Claims 9-12, 14, and 17-27 have been canceled in light of the restriction requirement. Claim 15 has also been canceled without prejudice and in light of the revisions to claims 1-4.

Claim 13 has been revised to correct an informality. New claims 28-37 have been introduced. They are supported at least by claim 16 and Figure 22 as originally filed.

New claims 38-39, dependent from claim 1, and new claims 40-41, dependent from claim 3, have been introduced. They are supported at least by Figure 22 as described above.

No new matter has been introduced, and entry of the revised claims is respectfully requested to leave claims 1-8, 13, 16, and 28-41 pending.

Formal Matters Regarding Sequence Compliance and Trademarks

The specification has been revised as indicated above to include sequence identifiers where believed to be necessary. The specification has also been revised to include

references to trademarks where believed to be applicable. No new matter has been introduced, and entry of the revised paragraphs is respectfully requested.

Restriction Requirement/Elected Invention

Applicants confirm the election of claims 1-8, 13, 15 and 16 as well as the election of the species of

(1) Daclizumab as the unmodified antibody.

(2) Positions 250 and 428, EU numbering, as a specific set of positions.

(3) Glutamine and leucine as the specific substitutions.

As previously pointed out, the sequences of certain heavy chains of modified Daclizumab are SEQ ID NOS. 119-128. The Daclizumab light chain is SEQ ID NO:118. SEQ ID NOS. 122 and 127 are IgG1 and IgG2 isotypes, respectively, of Daclizumab in which positions 250 and 428, EU numbering, are occupied by glutamine and leucine respectively (see positions 249 and 427 in SEQ ID NOs:122 and 127).

Applicants also wish to express their understanding that the search and examination of the elected species has been extended to include non-IgG1 isotypes. This is consistent with the nature of an election of species, where after search and examination of the elected species, the search and examination proceeds to one or more additional species.

Specifically, Applicants acknowledge the extended search and examination reflected in the alleged rejections based on Martin et al., which rejection is not limited to any IgG isotype.

The breadth of the search and examination is also evidenced by the Examiner's search strategy and search results for the instant application available through the U.S. Patent and Trademark Office (PTO) website. The non-sequence based search strategy and results were not limited by IgG isotype.

In light of the broad search and examination that has been conducted, Applicants acknowledge the search and examination of the claims for daclizumab and other IgG isotypes thereof.

Objection to Claim 4

Claim 4 was objected to as containing an informality due to the presence of two periods. The claim has been revised to correct this typographical error.

Alleged Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 4, and 15 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to recitations of "daclizumab, fontolizumab, visilizumab, and M200". As an initial matter, Applicants respectfully point out that the claims have been revised to feature daclizumab in correspondence with the Restriction Requirement and Applicants' election.

Applicants respectfully traverse because the terms must be read from the perspective of the skilled person and in light of the specification. In the case of "daclizumab", the term must be viewed in relation to the knowledge in the art regarding the variable region of daclizumab, such as that of U.S. Patent 5,530,101, as well as with regard to Figure 22 and its description in the instant application. With knowledge in the art regarding a variable region from daclizumab and the disclosure provided by the instant application, the definiteness and clarity of the claims do not require inclusion of variable region sequence information from daclizumab in revised independent claims 1 and 3. Therefore, Applicants respectfully submit that no issue of indefiniteness or ambiguity exists in the revised claims. In the absence of any issue, the instant rejection is misplaced, and may be properly withdrawn.

Applicants appreciate, however, the suggestion to include SEQ ID NOs to reflect inherent structural features of certain modified antibodies of the claims. Sequence identifiers were originally presented in claim 16, and are present in new claims 28-37.

Last, Applicants respectfully point out that "daclizumab" is not a trademark. Accordingly, no issue of indefiniteness is present by the use of the term in the above revised claims, especially in light of U.S. Patent 5,530,101.

Alleged Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 2, 4, and 15 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter "not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Applicants have carefully reviewed the statement of the rejection and understand it to be directed to the recitation of the "daclizumab" antibody in the claims. Applicants further understand it to include the Examiner's suggestion for either a biological deposit of the antibodies under the Budapest Treaty or inclusion of the sequence of the antibodies in their entireties. However, Applicants respectfully submit that given knowledge in the art regarding a variable region from daclizumab, as described in U.S. Patent 5,530,101, a requirement for either a biological deposit or inclusion of sequence information known in the art is misplaced.

It is well settled law that an application need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public (see MPEP 2164.05(a) and the cases cited therein). Therefore, there should be no requirement for inserting publicly accessible knowledge in the art in relation to the enablement standard because such knowledge is available for use in the practice of a claimed invention.

Applicants respectfully point out that knowledge regarding the sequence of a variable region from daclizumab is understood in the art and described in U.S. Patent 5,530,101. The claims have been revised to feature inclusion of such a variable region, which is present in an antibody according to the claims in combination with a heavy chain constant region that is modified at least at positions 250 and 428 (EU numbering) relative to an unmodified heavy chain constant region. Given this subject matter in the claims, and the knowledge in the art regarding daclizumab and antibody engineering in general, Applicants submit that ample description and guidance is present for the production and use of the claimed antibodies.

So contrary to the instant rejection, and in light of the level of knowledge available to the skilled person, Applicants respectfully submit that no basis exists to assert a lack

of enablement for making and using the instantly claimed invention. Accordingly, reconsideration and withdrawal of the instant rejection is respectfully requested.

Alleged Rejection Under 35 U.S.C. § 102

Claims 1, 3, 5-8, and 13 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Martin et al. as evidenced by Hinton et al. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of anticipation has been presented.

As an initial matter, Applicants point out that the instant rejection must be based on Martin et al. alone. The Hinton et al. reference is after the filing date of the instant application and so cannot serve as a basis for rejection under 35 U.S.C. § 102(b). Moreover, Hinton et al. also cannot be used to add disclosure to that by Martin et al. The standard set forth at MPEP 2131.01, and the court decisions cited therein, provide only three possible proper reasons to rely on an extra reference in a 35 U.S.C. § 102 rejection. None of the three relate to an extra reference (such as Hinton et al.) discussing a species not disclosed in the primary reference (Martin et al.).

The instant statement of the rejection, however, does not specify which of the three reasons from MPEP 2131.01 allows for the inclusion of Hinton et al. Instead, the statement of the rejection alleges that Hinton et al. describe subject matter as follows:

> "IgG mutants T250Q and M428L show increased binding to FcRn at pH 6.0 and no binding at pH 7.5 (see entire document, particularly page 6215, left column) and with an in vivo mean serum clearance rate about 1.8-1.9 fold lower than that of the corresponding unmodified antibody (e.g. see page 6216, left column)."

The above quote is clearly based upon Hinton et al.'s discussion of the particular "IgG mutants T250Q and M428L". But neither of these particular mutants are reported or discussed by Martin et al. So Hinton et al. is cited for its discussion of two species not found in

Martin et al. This inclusion of Hinton et al. is improper because 1) it attempts to inject the discussion of two particular species from Hinton et al. into the separate content of Martin et al.; and 2) it is irrelevant to the actual discussion in Martin et al., which does not include either of the two species. Accordingly, the reliance on Hinton et al. to allege an inherent property of subject matter discussed in Martin et al. is in error.

In light of the above, Applicants respectfully point out that inclusion of Hinton et al. lacks a proper basis and is improper. Because Martin et al. do not discuss the two particular species of Hinton et al., the two species and their characteristics cannot be add to Martin et al. Accordingly, the inclusion of Hinton et al. should be withdrawn, and this rejection may only be based on Martin et al. alone.

Moreover, Applicants point out that the claims have been revised to feature both a variable region from daclizumab and a modified heavy chain constant region. The pending claims are all directed to antibody polypeptide(s) that include a variable region from daclizumab.

This is in contrast to Martin et al.'s discussion of the use of a mutant, and heterodimeric, rat IgG2a Fc-only region to form a complex with rat FcRn as a model system (see page 867, right column, first full paragraph). There is no disclosure by Martin et al. of any variable region in their Fc-only polypeptides, and certainly no disclosure relating to a variable region from daclizumab.

It is well settled law that a case of anticipation requires a cited reference to teach every element of a claim (see MPEP 2131 and the cases cited therein). Given the factual differences between the claims and the Martin et al. reference, Applicants respectfully submit that no case of anticipation is present, and the instant rejection should be withdrawn.

Alleged Rejection Under 35 U.S.C. § 103

Claims 1-4, 13, 15, and 16 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Queen et al., in view of Martin et al. (as discussed above) and Krueger et al. Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

It is well settled law that a *prima facie* case of obviousness requires a suggestion or motivation to modify the cited references, the presence of a reasonable expectation of success in making the modification, and the disclosure or suggestion of all claim features (see MPEP 2143 to 2143.03 and the cases cited therein).

The instant statement of the rejection, however, fails to comply with all three of these requirements. With respect to a suggestion or motivation, the rejection alleges that it is present because

> "Queen et al. teach that anti-CD25 antibody has therapeutic effect in treating autoimmune disease, organ transplantation and any unwanted response by activated T-cells and Krueger et al. teach that daclizumab is anti-CD25 antibody; and Martin et al. teach that mutations at Fc region including positions 250 and 428 of an antibody would enhance its binding to FcRn resulting in prolonged serum half-life"

Applicants respectfully point out, however, that the above quote appears to be simply a listing of alleged teachings without any indication of why the teachings should be combined. For example, and contrary to the statement of the rejection, Applicants strongly disagree that "Martin et al. teach that mutations at Fc region including positions 250 and 428 of an antibody would enhance its binding to FcRn resulting in prolonged serum half-life" (underlining added).

A review of the relevant paragraph of Martin et al., starting on page 873 and ending on page 875, shows that the discussion of positions 250 and 428 therein merely provides a hope of modifications that "*may yield*" (in the case of position 250 and others) or "*could result*" in (in the case of position 428 and others) increased FcRn binding. With the use of phrases like "may yield" and "could result", Martin et al. do not meet the required standard for an adequate *motivation to make and use* molecules with the proffered modifications.

The mere offer of modifications to try is also shown by the fact that Martin et al. do not report any preparation or study of molecules modified at the indicated positions. Instead, the hypothetical modifications are presented in the context of a heterodimeric, rat IgG2a Fc-only

molecule for use in the Martin et al. model system. Such a system does not provide the necessary reasonable expectation of success in cases of a heavy chain constant region combined with a variable region.

In light of the foregoing, Applicants respectfully submit that no *prima facie* case of obviousness is present because no adequate motivation to combine the cited references to arrive at the claimed invention, and no reasonable expectation of success in making such a combination, are present. Accordingly this rejection is misplaced and may be properly withdrawn.

Alleged Rejections Based on Obviousness-Type Double Patenting

Claims 1-8, 13, 15, and 16 were provisionally rejected as unpatentable over claims 1-5, 8-12, 19-22, 25-28, 34-43, and 49 of commonly assigned, copending application 10/687,118; claims 1-4, 14, and 15 of commonly assigned, copending application 11/102,621; and claims 1-8, 13, 15 and 16 of commonly assigned, copending application 10/966,673. The statement of the rejection points out that a Terminal Disclaimer may be used to obviate this provisional rejection.

Applicants respectfully request that this provisional rejection be held in abeyance until the claims are otherwise allowable and the issue of obviousness-type double patenting is held as remaining.

Alleged Lack of Patentable Distinction

Claims 1-8, 13, 15, and 16 were held as "directed to an invention not patentably distinct" from claims 1-3, 5, 7-10, 12, 13, 15, and 17-19 of commonly assigned, copending application 10/966,673. While the statement of the allegation refers to the assertion of obviousness-type double patenting described above, Applicants respectfully point out that a different set of claims from application 10/966,673 are presented. Applicants respectfully suggest that confirmation of the claims involved may be needed.

The statement of the allegation appears to request a showing that the instant application and copending application 10/966,673 were commonly owned at the time *the invention in the instant application was made.*

Applicants respectfully point out, however, that the instant application has a filing date of April 9, 2004 while copending application 10/966,673 has a *later* filing date of October 15, 2004. Accordingly, Applicants are uncertain as to the basis of the determination that the invention in application 10/966,673 was in existence, and therefore could be co-owned, at the time of the instant invention.

Despite the uncertainty, and in the interest of advancing prosecution, Applicants submit that the invention of copending application 10/966,673 was commonly assigned, or subject to the same duty to assign, with the invention of the instant application at the time the invention in copending application 10/966,673 was made.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,

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